Title: **Seeking Ligands for Lonely Orphan Receptors.**

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Source: Science; 05/21/99, Vol. 284 Issue 5418, p1285, 2p, 1 diagram

Document Type: Article

Subject(s): NUCLEAR receptors (Biochemistry) -- Physiological effect
CELL receptors
LIGANDS (Biochemistry) -- Physiological effect
BILE acids -- Physiological effect

Abstract: Discusses research which showed that bile acids are the physiological ligands of the farnesoid X receptor (FXR). Role of nuclear receptors in the reaction of cells to chemicals; Defining orphan nuclear receptors and their ligands; Value of drugs that could mimic such ligands; Research in this issue by Willson et al, and by Mangelsdorf et al; Role of FXR in the regulation of biochemical pathways; Most important bile acids in humans.

Full Text Word Count: 1581

ISSN: 0036-8075

Accession Number: 1874687

Persistent Link to this Article: http://search.epnet.com/direct.asp?an=1874687&db=bch

Database: Business Source Corporate

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Section: ***SCIENCE'S*** COMPASS

SEEKING LIGANDS FOR LONELY ORPHAN RECEPTORS

Cells are exposed to a plethora of chemicals--metabolic intermediates, hormones, and compounds in the environment. One way in which cells adapt to these physiological and toxicological challenges is through nuclear receptors, which bind to these molecules, move to the nucleus, and initiate changes in gene transcription. Currently we know of about 70 different nuclear receptors, but only half of these have ligands that have been identified (1). The remaining receptors with unknown ligands are called orphan nuclear receptors. Identifying ligands for these receptors is a huge challenge but is one that the pharmaceutical industry is eager to take on. Drugs that mimic such ligands could be of particular value in the treatment of diseases that are caused by defects in the biochemical pathways in which these nuclear receptors are involved.

Two reports on pages 1362 and 1365 of this issue from the groups of Willson and Mangelsdorf (2,3) and one in this month's Molecular Cell (4) now show that bile acids, important regulators of cholesterol homeostasis, are the physiological ligands of the farnesoid X receptor (FXR), an orphan member of the nuclear receptor family. This finding implicates FXR in the regulation of one of the key biochemical pathways in the body.

The most important primary bile acids in humans are cholic acid (the most abundant) and chenodeoxycholic acid. Bile acids are oxidation products of cholesterol with the enzyme cholesterol 7 Alpha-hydroxylase as the rate-limiting step in their synthesis. Cholic acid and chenodeoxycholic acid differ only in that cholic acid has a hydroxyl group at the 12 Alpha position and requires an extra enzyme, 12 Alpha-hydroxylase, for synthesis. Bile acids have two important functions in the gut: to facilitate solubilization and disposal of cholesterol (see the figure) and to facilitate absorption of dietary fat and fat-soluble vitamins. They are synthesized from cholesterol by two distinct pathways. The first is the classical "neutral" pathway in which cholesterol 7 Alpha-hydroxylase catalyzes the first and rate-limiting step (5). In the second (and more recently discovered) "acidic" pathway (6), oxysterol 7 Alpha-hydroxylase replaces cholesterol 7 Alpha-hydroxylase as the primary

synthetic enzyme (5). The acidic pathway begins with the oxidation of a cholesterol side chain to form 27-hydroxy cholesterol. Although the neutral pathway usually predominates, the acidic pathway is important, for example, in babies with a mutation in the oxysterol 7 Alpha-hydroxylase gene (7). The three reports now demonstrate that chenodeoxycholic acid but not cholic acid binds to FXR (2-4). Moreover, when bound to bile acids, FXR down-regulates the transcription of cholesterol 7 Alpha-hydroxylase and activates the gene encoding a candidate bile acid transporter protein, which transports bile acids from the gut to the liver (3). The result is a decrease in the amount of bile acid in the gut. Hence, through binding to FXR, bile acids can regulate their own synthesis and transport.

One of the most notable findings is that chenodeoxycholic acid, not cholic acid, is the principal ligand of FXR. Chenodeoxycholic acid is therefore a crucial regulator of cholesterol 7 Alpha-hydroxylase expression and of cholesterol homeostasis (its regulatory effect on cholesterol levels has been known for decades) (8,9). The enzyme that catalyzes the synthesis of cholic acid, 12 Alpha-hydroxylase, is thus an important branch point enzyme and potential feedback mechanism in bile acid biosynthesis because it regulates the ratio of cholic acid to chenodeoxycholic acid.

The affinity (K_d) of FXR binding to bile acids is in the micromolar range, about three orders of magnitude higher than the nanomolar K_d values for steroid hormone receptors bound to their ligands. Micromolar K_d values have been observed for other orphan nuclear receptors: the peroxisomal proliferator activated receptor (PPAR), which binds fatty acids, and the liver X receptor (LXR Alpha), which binds oxysterols. These high K_d values are consistent with the relatively high tissue concentrations of the lipid ligands of these receptors. Clearly, nuclear receptors should no longer be regarded exclusively as high-affinity receptors, because FXR, PPAR, and LXR Alpha all bind their ligands with relatively low affinity.

We still do not understand the mechanisms that regulate the expression of oxysterol 7 Alpha-hydroxylase (the principal enzyme of the alternative pathway of bile acid synthesis) and 12 Alpha-hydroxylase, or the parts played by other orphan receptorsin the regulation of cholesterol homeostasis. It is well established that, when bound to its ligand, LXR Alpha can induce the synthesis of cholesterol 7 Alpha-hydroxylase, thus opposing the effect of FXR. The ligand for LXR Alpha is not bile acid but oxysterol (10), an oxidized metabolite of cholesterol. Mice genetically engineered to be deficient in LXR Alpha appear to be normal, but when they are fed a very high cholesterol diet their livers become full of cholesterol (10). As animals deficient in 7 Alpha-hydroxylase survive without evident problems, does this mean that oxysterol 7 Alpha-hydroxylase can replace cholesterol 7 Alpha-hydroxylase under normal dietary conditions? It is noteworthy that LXR Alpha and FXR, which have opposing effects on cholesterol 7 Alpha-hydroxylase synthesis, communicate directly with each other (4). In the presence of FXR, bile acids repress transcriptional activity of LXR Alpha, but they have no effect in the absence of FXR.

Another player in the story of the regulation of cholesterol and bile acid synthesis is PPAR Alpha. When bound to fatty acids, PPAR Alpha stimulates the proliferation of peroxisomes and induces synthesis of several enzymes involved in the Beta-oxidation of fatty acids. PPAR Alpha is not only activated by fatty acids but also by lipid-lowering drugs, such as the fibrates, which stimulate proliferation of peroxisomes (11). Peroxisomes catalyze the Beta-oxidation of fatty acids, the synthesis of cholesterol and other isoprenoids, and certain steps in the oxidation of cholesterol to bile acids. Interestingly, FXR was originally identified as a receptor for farnesol, an intermediate in the synthesis of cholesterol and other isoprenoids by peroxisomes (12). FXR, LXR Alpha, and PPAR Alpha may therefore regulate both fatty acid and cholesterol homeostasis. These two pathways are probably coregulated because the amount of free fatty acids and cholesterol in cells is increased when cholesterol esters (delivered by low density lipoproteins to lysosomes) are hydrolyzed into their component parts (cholesterol and fatty acids). The cell has to take care of both of these potentially toxic molecules at the same time suggesting that the pathways for disposal of cholesterol should be coordinated with those involved in fatty acid disposal.

Receptors for hormones such as glucocorticoids, estrogen, and thyroid hormone also regulate cholesterol homeostasis. Another orphan receptor, the pregnane X receptor (PXR), down-regulates cholesterol 7 Alpha-hydroxylase expression and increases bile acid flow (13). This promiscuous receptor is activated by many pharmaceutical agents. Its most effective endogenous ligand is corticosterone, and one of its most potent pharmaceutical ligands is the antibiotic rifampicin. Interestingly, the ansamycins, which are derived from rifampicin but lack antibacterial activity, are hypolipidemic agents that effectively lower plasma cholesterol levels, perhaps by binding to PXR.

The 70 different nuclear receptors characterized thus far may be just a small sampling of a much larger family. A recent scan of the Caenorhabditis elegans genome for two-zinc finger structures (a characteristic feature of nuclear receptors) reveals the presence of 228 such proteins in this nematode (14). It is, of course, not clear that mammalian homologs for all of these nematode nuclear receptors exist. However, it is tempting to speculate that there are many more nuclear receptors and their ligands waiting to be discovered.

DIAGRAM: Bilious biochemical pathways. A number of nuclear receptors are involved in the biochemical pathways that regulate cholesterol homeostasis. For example, FXR binds bile acids that are important in the disposal of cholesterol. When bound to bite acids, FXR switches off (-) production of cholesterol 7 Alpha-hydroxylase (which is the rate-limiting step in bite acid synthesis) and switches on (+) synthesis of bite acid transporter proteins, leading to a decrease in bite acid in the gut and an increase in cholesterol levels in the blood. Another nuclear receptor, LXR Alpha, which binds oxysterols, induces the synthesis of bite acids by up-regulating (+) cholesterol 7 Alpha-hydroxylase. In addition to the classical pathway of bile acid synthesis, there is an alternative pathway in which oxysterol 7 Alpha-hydroxylase is the rate-limiting enzyme.

R f renc s

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Source: Science, 05/21/99, Vol. 284 Issue 5418, p1285, 2p
Item: 1874687

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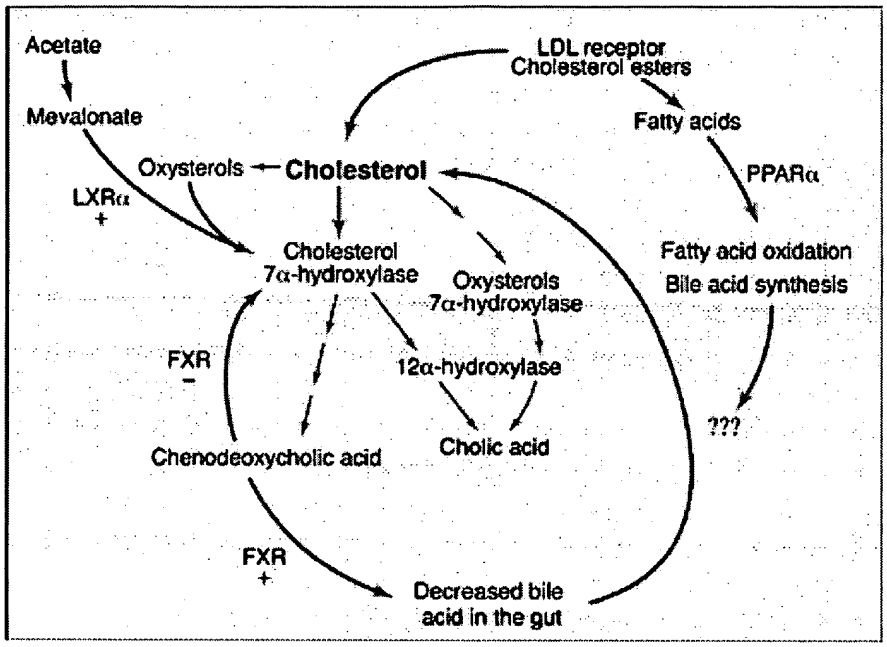

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Volume 284, Number 5418, Issue of 21 May 1999, p. 1285.

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